Seizures after single-agent overdose with pharmaceutical drugs: analysis of cases reported to a poison center

Reichert, C ; Reichert, P ; Monnet-Tschudi, F ; Kupferschmidt, H ; Ceschi, A ; Rauber-Lüthy, C

Abstract: CONTEXT Seizures during intoxications with pharmaceuticals are a well-known complication. However, only a few studies report on drugs commonly involved and calculate the seizure potential of these drugs. OBJECTIVES To identify the pharmaceutical drugs most commonly associated with seizures after single-agent overdose, the seizure potential of these pharmaceuticals, the age-distribution of the cases with seizures and the ingested doses. METHODS A retrospective review of acute single-agent exposures to pharmaceuticals reported to the Swiss Toxicological Information Centre (STIC) between January 1997 and December 2010 was conducted. Exposures which resulted in at least one seizure were identified. The seizure potential of a pharmaceutical was calculated by dividing the number of cases with seizures by the number of all cases recorded with that pharmaceutical. Data were analyzed using descriptive statistics. RESULTS We identified 15,441 single-agent exposures. Seizures occurred in 313 cases. The most prevalent pharmaceuticals were mefenamic acid (51 of the 313 cases), citalopram (34), trimipramine (27), venlafaxine (23), tramadol (15), diphenhydramine (14), amitriptyline (12), carbamazepine (11), maprotiline (10), and quetiapine (10). Antidepressants were involved in 136 cases. Drugs with a high seizure potential were bupropion (31.6%, seizures in 6 of 19 cases, 95% CI: 15.4-50.0%), maprotiline (17.5%, 10/57, 95% CI: 9.8-29.4%), venlafaxine (13.7%, 23/168, 95% CI: 9.3-19.7%), citalopram (13.1%, 34/259, 95% CI: 9.5-17.8%), and mefenamic acid (10.9%, 51/470, 95% CI: 8.4-14.0%). In adolescents (15-19y/o) 23.9% (95% CI: 17.6-31.7%) of the cases involving mefenamic acid resulted in seizures, but only 5.7% (95% CI: 3.3-9.7%) in adults (20y/o; $p < 0.001$). For citalopram these numbers were 22.0% (95% CI: 12.8-35.2%) and 10.9% (95% CI: 7.1-16.4%), respectively ($p = 0.058$). The probability of seizures with mefenamic acid, citalopram, trimipramine, and venlafaxine increased as the ingested dose increased. CONCLUSIONS Antidepressants were frequently associated with seizures in overdose, but other pharmaceuticals, as mefenamic acid, were also associated with seizures in a considerable number of cases. Bupropion was the pharmaceutical with the highest seizure potential even if overdose with bupropion was uncommon in our sample. Adolescents might be more susceptible to seizures after mefenamic acid overdose than adults. "Part of this work is already published as a conference abstract for the XXXIV International Congress of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) 27-30 May 2014, Brussels, Belgium." Abstract 8, Clin Toxicol 2014;52(4):298.

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Seizures after single-agent overdose with pharmaceutical drugs: Analysis of cases reported to a poison centre

Cornelia Reichert[1], Peter Reichert[2], Florianne Monnet-Tschudi[3], Hugo Kupferschmidt[1], Alessandro Ceschi[1,4], Christine Rauber-Lüthy[1]

[1]Swiss Toxicological Information Centre, Associated Institute of the University of Zürich, Switzerland.
[2]Eawag, Swiss Federal Institute of Aquatic Science and Technology, Dübendorf, Switzerland.
[3]Department of Physiology and Swiss Centre for Applied Human Toxicology, University of Lausanne, Switzerland.
[4]Department of Clinical Pharmacology and Toxicology, University Hospital Zürich, Switzerland

Key words Poisoning; Convulsions; Seizure potential; Age-dependency; Adolescents.

Abbreviations AD, antidepressant; CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor; STIC, Swiss Toxicological Information Centre; TCA, tricyclic antidepressant.

Address correspondence to Cornelia Reichert, Swiss Toxicological Information Centre, Associated Institute of the University of Zürich, Freiestrasse 16, CH-8032 Zürich, Switzerland. Tel: +41-44-251-6666. Fax: +41-44-252-8833. E-mail: cornelia.reichert@usz.ch.

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Abstract

*Context. S*eizures during intoxications with pharmaceuticals are a well-known complication. However, only a few studies report on drugs commonly involved and calculate the seizure potential of these drugs. *Objectives.* To identify the pharmaceutical drugs most commonly associated with seizures after single-agent overdose, the seizure potential of these pharmaceuticals, the age-distribution of the cases with seizures and the ingested doses. *Methods.* A retrospective review of acute single-agent exposures to pharmaceuticals reported to the Swiss Toxicological Information Centre (STIC) between January 1997 and December 2010 was conducted. Exposures which resulted in at least one seizure were identified. The seizure potential of a pharmaceutical was calculated by dividing the number of cases with seizures by the number of all cases recorded with that pharmaceutical. Data were analyzed by descriptive statistics. *Results.* We identified 15 441 single-agent exposures. Seizures occurred in 313 cases. The most prevalent pharmaceuticals were mefenamic acid (51 of the 313 cases), citalopram (34), trimipramine (27), venlafaxine (23), tramadol (15), diphenhydramine (14), amitriptyline (12), carbamazepine (11), maprotiline (10) and quetiapine (10). Antidepressants were involved in 136 cases. Drugs with a high seizure potential were bupropion (31.6%, seizures in 6 of 19 cases, 95% CI 15.4-50.0%), maprotiline (17.5%, 10/57, 95% CI 9.8-29.4%), venlafaxine (13.7%, 23/168, 95% CI 9.3-19.7%), citalopram (13.1%, 34/259, 95% CI 9.5-17.8%) and mefenamic acid (10.9%, 51/470, 95% CI 8.4-14.0%). In adolescents (15-19y/o) 23.9% (95% CI 17.6-31.7%) of the cases involving mefenamic acid resulted in seizures, but only 5.7% (95% CI 3.3-9.7%) in adults (≥20y/o) ($p<0.001$). For citalopram these numbers were 22.0% (95% CI 12.8-35.2%) and 10.9% (95% CI 7.1-16.4%), respectively ($p=0.058$). The probability of seizures with mefenamic acid, citalopram, trimipramine and venlafaxine increased as the ingested dose increased. *Conclusions.* Antidepressants were frequently associated with seizures in overdose,

but other pharmaceuticals, as mefenamic acid, were also associated with seizures in a considerable number of cases. Bupropion was the pharmaceutical with the highest seizure potential even if overdose with bupropion was uncommon in our sample. Adolescents might be more susceptible to seizures after mefenamic acid overdose than adults.

Introduction

Drug-related seizures account for 1.7 to 14% of all cases with acute symptomatic seizures.[1-3] In a study from the California Poison Control System the rate of complications associated with drug-induced seizures was 60%.[4] Complications as defined by the authors were a prolonged hospital stay, endotracheal intubation, status epilepticus, anoxic brain injury or death. Despite these facts epidemiologic data are rare and only a few studies address the problem of overdose-induced seizures.[5] In four studies the incidence rates of seizures after poisoning are reported to be between 1.3 and 5.2%.[6-9] Five studies analyze the substances involved in poisoning-induced seizures.[4,6,9-11] In all of them antidepressants were among the most frequent drugs and rates between 28.8 and 42.4% are reported. In four of the studies bupropion was the most prevalent pharmaceutical reported to cause seizures with rates between 14.9 and 23% of all cases.[4,6,9,10] The studies published so far include cases with single-agent exposures and mixed-ingestions. Coingestants are reported in 18.4-42% of the cases.[4,6,10,11]

The aim of this study was to further the understanding of drug-induced seizures. We examined which pharmaceutical exposures are commonly associated with overdose-induced seizures and the potential of these pharmaceuticals to cause seizures. Furthermore we calculated the percentage of cases with seizures for different age groups and compared the rates of adolescents (15-19 years of age) and adults (≥20 years of age). To the best of our knowledge, there are no studies that describe these aspects in single-agent overdoses with pharmaceuticals.

Methods

Data collection

The Swiss Toxicological Information Centre (STIC) provides medical advice concerning poisonings to the general public and to health professionals on a 24/7 basis.

All calls to the STIC are recorded in an in-house database system. Collected data include age, weight and sex of the patient, circumstances of poisoning, ingested dose, clinical effects,

temporal course of the poisoning, results of drug screening and laboratory analysis, clinical parameters, decontamination and treatment measures, antidotes given and medical complications.

Study design

The study was conducted as a retrospective single-centre review of consecutive single-agent overdoses with pharmaceutical drugs reported to the STIC between January 1, 1997 and December 31, 2010.

Inclusion criteria

We included all acute human single-agent overdoses with a pharmaceutical drug intended for human use. Furthermore a written feedback by a physician, providing sufficient data about clinical effects and evolution, had to be available. Among all single-agent overdoses we identified cases with occurrence of seizures by searching the data files for key words as epileptic, seizures or convulsions.

Only cases with a confirmed or likely causal relationship between exposure and clinical effects were considered. Causality is determined by the following criteria: Cases with a likely causality are defined as having a clear temporal relationship between ingestion and clinical effects, absence of other reported drugs or absence of diseases which could explain the clinical effects and presence of symptoms which are described for the substance or are plausible from a pharmacodynamic point of view. Cases which fulfill the above mentioned criteria and have in addition an analytical detection (qualitative or quantitative) of the substance in a body fluid are defined as confirmed. Causality of asymptomatic cases without analysis of body fluids cannot be classified according to the above mentioned criteria. We included these cases according to the reported ingested substance.

Ethics approval

Ethics approval was not required due to the nature of the study design according to the regulations of the Cantonal Ethics Committee Zürich, Switzerland.

Data analysis

Confidence intervals (CI) of seizure rates were estimated using the technique described by Wilson[12] as recommended in the applied statistical literature.[13,14] Statistical tests of binomial coefficients were done using Fisher's exact test, those comparing dose samples by the non-parametric Wilcoxon-Mann-Whitney rank-sum test. All data evaluations were performed using the statistics and graphics software R.[15] P-values <0.05 were considered statistically significant.

The seizure rates in different age groups were calculated by dividing the number of reported cases associated with seizures in an age group by the number of all cases in the same age group.

The seizure potential of a pharmaceutical was calculated by dividing the number of cases associated with seizures by the number of all cases recorded with that drug.

Results

The STIC answered a mean of 31 927 calls per year (range 29 506-34 283) during the study period. The referral population was about 7.1 million people at the beginning and about 7.8 million people at the end of the study period.

Over the 14 year study period 15 441 cases met the inclusion criteria. The patients were between 1 day and 98 years old (Table 1). There were 65.0% female and 32.1% male patients. Gender was not reported in 2.9% of the cases. Cases with accidental exposure (34.4%), intentional exposure (64.3%) and exposure by other reasons (1.3%) were recorded. Intentional exposures were mostly suicidal or abusive, exposure by other reasons include iatrogenic exposures or exposures with unknown reason. Analytical confirmation (quantitative or qualitative) was available in 9.2% of the cases.

At least one seizure was recorded in 313 of the cases. The patients were between 1 and 90 years old (Table 1). There were 70.0% female and 29.7% male patients. Gender was not reported in 0.3% of the cases with seizures. Cases with accidental exposure (13.4%), intentional

exposure (85.0%) and exposure by other reasons (1.6%) were recorded. Analytical confirmation (quantitative or qualitative) was available in 15.3% of the cases with seizures.

In the 313 cases with seizures 61 different pharmaceutical drugs were involved. Nineteen drugs were associated with three or more cases with seizures (Figure 1). The most prevalent drug was mefenamic acid (51 cases, 16.3%), followed by citalopram (34 cases, 10.9%), trimipramine (27 cases, 8.6%), venlafaxine (23 cases, 7.3%), tramadol (15 cases, 4.8%), diphenhydramine (14 cases, 4.5%), amitriptyline (12 cases, 3.8%), carbamazepine (11 cases, 3.5%), maprotiline (10 cases, 3.2%), quetiapine (10 cases, 3.2%), fluoxetine (9 cases, 2.9%), dextromethorphan (8 cases, 2.6%), chlorprothixene (8 cases, 2.6%), bupropion (6 cases, 1.9%), tolperisone (5 cases, 1.6%), clozapine (4 cases, 1.3%), clomipramine (4 cases, 1.3%), olanzapine (3 cases, 1.0%) and methadone (3 cases, 1.0%). These 19 pharmaceuticals were responsible for 82% (257/313) of all cases. The seizures in the remaining 56 cases were associated with 42 further drugs with 14 pharmaceuticals associated with two cases with seizures each (bupivacaine, clotiapine, codeine, dibenzepin, doxepin, fluvoxamine, ioxaglic acid, isoniazid, lamotrigine, lidocaine, opipramol, phenobarbital, propranolol and verapamil) and a wide variety of 28 pharmaceuticals associated with one case with seizures each (see online supplementary data). Antidepressants (AD) were associated with 136 cases with seizures (43.5%), antipsychotics with 30 (9.6%) and antiepileptics with 17 (5.4%) cases (Table 2).

The highest seizure potential was found with bupropion. Seizures were recorded in 31.6% (6/19 cases; 95% CI 15.4-54.0%). It was followed by maprotiline 17.5% (10/57 cases; 95% CI 9.8-29.4%), venlafaxine 13.7% (23/168 cases; 95% CI 9.3-19.7%), citalopram 13.1% (34/259 cases; 95% CI 9.5-17.8%) and mefenamic acid 10.9% (51/470 cases; 95% CI 8.4-14.0%) (Figure 2).

The 313 cases with seizures result in a seizure rate of 2.0% (313/15 441). For seizure rates in the different age groups see Table 1. The difference between the rate of 4.3% in adolescents (15-19y/o) and the rate of 2.3% in adults (≥20y/o) is statistically significant ($p<0.001$). Regarding this age-difference we calculated the rates for the four pharmaceuticals with most seizure cases.

For mefenamic acid the difference of the rates between adolescents 23.9% (95% CI 17.6-31.7%) and adults 5.7% (95% CI 3.3-9.7%) was significant ($p<0.001$).. For citalopram the seizure rates for adolescents and adults were 22.0% (95% CI 12.8-35.2%) and 10.9% (95% CI 7.1-16.4%), respectively ($p=0.058$). No age-difference could be found for trimipramine ($p=0.73$) and venlafaxine ($p=0.48$). If we exclude the 51 cases with mefenamic acid from the 313 cases, the difference in rates between adolescents and adults was no more significant ($p=0.17$). The seizure rates for adolescents and adults were 2.8% (95% CI 2.1-3.7%) and 2.2% (95% CI 1.9-2.6%), respectively.

To exclude a dose-effect causing the age-difference in mefenamic acid and citalopram cases, we calculated the medians of the reported ingested doses for the two drugs. There was no significant difference of the doses between adolescents and adults. For mefenamic acid the median doses were 8.5g (131.1mg/kg) in adolescents and 10.0g (130.3mg/kg) in adults ($p=0.39$ for dose in g, $p=0.74$ for dose in mg/kg). Dose as reported by the patient or a caregiver was available in 92.2% of the cases with seizures and in 84.7% of all cases. The median of the ingested doses for citalopram were 1.0g (15.6mg/kg) and 1.3g (19.7mg/kg), respectively ($p=0.35$ and 0.70). Dose as reported by the patient or a caregiver was available in 85.3% of the cases with seizures and in 86% of all cases.

Table 3 shows the ranges and medians of the ingested doses of the four pharmaceuticals most commonly associated with seizures. The probability of seizures increased as the dose increased and the difference between the medians of the ingested doses in cases with and without seizures was significant with $p<0.001$ for each of the four agents.

Discussion

Drugs involved

In the literature only case series are reported which include cases with co-ingestants, no studies were found which analyze only single-agent overdoses associated with drug-induced seizures. In case series the authors assigned the drug with an already described seizure risk to be the

likely cause of the convulsions in cases with multi-drug exposures.[4,6,10,11] This could bias the results in cases with ingestion of more than one substance described to cause seizures or in cases with new substances not yet known to cause seizures which are co-ingested with substances with a known seizure risk. The fact that we only considered single-agent exposures strengthens the causal association between the seizures and the ingested pharmaceutical.

As in the present study, all studies so far found high rates of seizures associated with antidepressants (28.8-42.4%).[4,6,9-11] Antidepressants are known to have a considerable potential to cause seizures in overdose, some agents having a seizure rate of >10%.[16]

However, the pharmaceutical most often associated with drug-induced seizures in the present study was mefenamic acid. This non-steroidal anti-inflammatory drug (NSAID) is widely available as an analgesic in Switzerland and a few other countries, but not in the USA and therefore was probably not reported in the aforementioned studies. The other pharmaceuticals which were associated with seizures in more than 5% of the cases in our study are also described in the literature. Thundiyil et al[4] found the seizure rate for cases with citalopram/escitalopram overdose to be 8.3% and the one for venlafaxine 1.7%. In a another study by Thundiyil et al[10] the seizure rate for venlafaxine was 6%. The proportion of trimipramine-induced seizure is not described in the literature, but in three studies rates of seizures induced by tricyclic antidepressants were between 1.7 and 24.6%.[4,10,11]

Seizure potential

A high number of cases with seizures associated with a particular drug could mean that this drug has a high seizure potential or that it is more often involved in overdose, or both. The studies which analyzed cases with seizures reported so far do not report data about the corresponding cases with the same substance without occurrence of seizures during the time interval studied, therefore seizure potentials cannot be calculated.[4,6-11] However, there are some studies analyzing clinical effects in overdose of single substances or of drug classes that mention seizure potentials.[17-21] In our study the highest seizures potential was reached by bupropion.

Bupropion overdose was a rare event with only 19 exposures, but these intoxications were associated with seizures in six of the cases. Bupropion is known to frequently cause seizures in overdose[18,22] and it was the single drug causing most seizures in three studies.[4,9,10] Despite the small number of cases our analysis confirms the high potential of bupropion to cause seizures in overdose. For maprotiline, venlafaxine, citalopram and mefenamic acid we found a seizure potential of more than 10%. This considerable risk of seizures in overdose is described in the literature. Seizures occurred in more than 10% of acute maprotiline intoxications,[16,20,23] in 4-13.7% of venlafaxine intoxications,[19,20,24-27] in 5.8-15.9% of citalopram intoxications[20,21,28-30] and in 14-39.3% of mefenamic acid intoxications.[17,31-33]

Seizure rates and age distribution

In the literature rates of seizures associated with intoxications are reported in four case series.[6-9] In a recent study with cases reported to a toxico-surveillance system seizures occurred in 4.7% of the patients younger than 18 years and in 4.5% of the adult patients.[6] In a retrospective review 1.6% of 1561 children (3-172 months) admitted for intoxication developed seizures.[7] In another retrospective review seizures occurred in 1.3% of 3687 children (0-18 years) admitted to a pediatric toxicology department.[8] In a case series with adults 5.2% of 2340 patients admitted to a poisoning treatment centre had seizures.[9] In all four case series also multiple-agent exposures were analyzed and substances other than pharmaceutical drugs were included. In our study, which is one of the largest to date describing seizure rates in cases with overdose, we found very low seizure rates of 0.4 and 0.6% in children of 0-4 and 5-9 years of age, respectively. In poisonings, seizure rates in children are expected to be lower than in adults since intoxications in children less than 10 years of age are almost exclusively accidental and smaller doses are ingested than in intentional poisonings. The seizure rate of all patients from 0-19 years of age was 1.7% and is comparable to the data given by Citak (1.6%)[7] and Nitescu (1.3%)[8], but lower than the one reported by Finkelstein (4.7%).[6] The seizure rate of 2.3% we found in adults (≥20 y/o) is lower than the rates reported by Kirschner (5.2%)[9] and Finkelstein

(4.5%).[6] The differences might be due to our strict inclusion criteria (only single-agent exposures, only pharmaceutical drugs), but could also be a consequence of other reasons, as ingestion of different amounts or substances or a different patient collective.

One interesting result of our study is the higher seizure rate in adolescents (15-19 y/o) compared to adults (≥20y/o), which is almost exclusively due to the cases with mefenamic acid. An age-dependency of seizures in mefenamic acid overdose has already been described earlier. In a case series seizures were seen in 22.3% of the cases in 16-20 year olds, but only in 7.1% of patients older than 20 years of age.[33] Also in the cases with citalopram adolescents had more seizures than adults, but this difference was statistically not significant. The most obvious reason for an apparent age-dependency of seizures would be that adolescents could have ingested higher doses, since a dose-dependency for occurrence of seizures is well described.[22,30,34] However, we could not find a significant difference of the medians of the ingested doses of mefenamic acid or citalopram in the two groups. Furthermore, adolescents could genuinely be more susceptible to seizures. It is known that during adolescence important changes take place in the brain, such as remodeling of synaptic connections.[35] There is also some evidence from animal models that during adolescence susceptibility to seizures is increased[36,37] and reported annual incidence rates of epilepsy are higher in patients of 10-19 years of age than in adults.[38]

Ingested dose and probability of seizures

Dose-dependency of occurrence of seizures is well-known in cases of drug overdose[34] and is reported in the literature for mefenamic acid,[17,32,33] citalopram, [21,28,29] trimipramine [39] and venlafaxine.[19] The results in the literature and of our study support the mechanistic view of the pathophysiology of seizures in overdose which are thought to be provoked by overexcitation of the brain by different pathways in a dose-dependent manner.[5,40]

Limitations

This study has several limitations due to the inherent nature of poison centre data.[41] The study has a retrospective design and certain information might be missing in some of the cases. Some

clinical effects might be underreported, but seizures are an obvious effect and recording is quite probable. Reporting to poison centres is voluntary and the seizure rate could be overestimated since the poison centre might not be called for advice in cases with minor ingestions or in cases with substances the treating physician is familiar with. The ingested substances are based mainly on reports of the patient or caregivers in cases involving children. Analytical confirmation was available only in a minority of the cases, so we cannot exclude definitely that other substances have been co-ingested. We did not consider factors as dose, age or comorbidities in calculating the seizure potential which could influence the result. So it cannot be excluded that pharmaceuticals with a high seizure potential were taken in a higher relative dose or by a different age group than drugs with a lower seizure potential. But the drugs we found to have a high seizure potential are described in the literature as frequently causing seizures in overdose. Our results can only partly be generalized as the frequency of use of pharmaceutical drugs may vary considerably among different countries. Our strict inclusion/exclusion criteria with exclusion of multiple-agent exposures result in smaller case numbers. However, the inclusion of only single-agent exposures favors a correct interpretation of the results, seizures do not have to be assigned to one of the drugs ingested and interactions between different pharmaceuticals can be excluded.

Conclusions

Our study confirms that antidepressants play an important role in overdose-induced seizures, many substances with a high seizure potential are found in this drug class. But a variety of other pharmaceutical drugs, as mefenamic acid can also be frequently associated with seizures in overdose. The most frequent pharmaceuticals associated with seizures do not necessarily have the highest seizure potential. This was shown for bupropion, which has a very high seizure potential, but was only involved in 1.9% of the cases with seizures, in comparison to mefenamic acid, which was the most prevalent drug associated with seizures, but has a lower seizure

potential than bupropion. Adolescents were more likely to develop seizures than adults with mefenamic acid. This finding deserves further consideration for other substances. The probability of seizures with mefenamic acid, citalopram, trimipramine and venlafaxine increased as the ingested dose increased.

Declaration of interest

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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References

1. Beleza P. Acute symptomatic seizures: a clinically oriented review. Neurologist 2012;18:109-19.
2. Messing RO, Closson RG, Simon RP. Drug-induced seizures: a 10-year experience. Neurology 1984;34:1582-6.
3. Pesola GR, Avasarala J. Bupropion seizure proportion among new-onset generalized seizures and drug related seizures presenting to an emergency department. J Emerg Med 2002;22:235-9.
4. Thundiyil JG, Rowley F, Papa L, Olson KR, Kearney TE. Risk factors for complications of drug-induced seizures. J Med Toxicol 2011;7:16-23.
5. Wills B, Erickson T. Chemically induced seizures. Clin Lab Med 2006;26:185-209.
6. Finkelstein Y, Hutson JR, Freedman SB, Wax P, Brent J. Drug-induced seizures in children and adolescents presenting for emergency care: Current and emerging trends. Clin Toxicol (Phila) 2013;51:761-6.
7. Citak A, Soysal DD, Ucsel R, Karabocuoglu M, Uzel N. Seizures associated with poisoning in children: tricyclic antidepressant intoxication. Pediatr Int 2006;48:582-5.
8. Nitescu VG, Ulmeanu AI, Vivisenco IC, Babaca D, Ulmeanu CE. Seizures in Acute Poisoning in Children - 5 Year Study. Clin Toxicol 2010;48:248.
9. Kirschner RI, Cimikoski WJ, Squillante CM, Donovan JW. Drugs Associated with Seizure in Patients Admitted to a Toxicology Treatment Center. Clin Toxicol 2008;46:600.
10. Thundiyil JG, Kearney TE, Olson KR. Evolving epidemiology of drug-induced seizures reported to a Poison Control Center System. J Med Toxicol 2007;3:15-9.
11. Olson KR, Kearney TE, Dyer JE, Benowitz NL, Blanc PD. Seizures associated with poisoning and drug overdose. Am J Emerg Med 1994;12:392-5.
12. Wilson EB. Probable inference, the law of succession, and statistical inference. J Am Stat Assoc 1927;22:209-12.
13. Agresti A, Coull BA. Approximate is better than "exact" for interval estimation of binomial proportions. Am Stat 1998;52:119-26.
14. Brown LD, Cai TT, DasGupta A, et al. Interval estimation for a binomial proportion - Comment - Rejoinder. Stat Sci 2001;16:101-33.
15. R Development Core Team (2008). R: A language and environment for statistical computing. R Foundation for Statistical Computing V, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org.
16. Judge BS, Rentmeester LL. Antidepressant overdose-induced seizures. Neurol Clin 2011;29:565-80.
17. Balali-Mood M, Critchley JA, Proudfoot AT, Prescott LF. Mefenamic acid overdosage. Lancet 1981;1:1354-6.
18. Belson MG, Kelley TR. Bupropion exposures: clinical manifestations and medical outcome. J Emerg Med 2002;23:223-30.
19. Kumar VVP, Isbister GK, Duffull SB. The effect of decontamination procedures on the pharmacodynamics of venlafaxine in overdose. Br J Clin Pharmacol 2011;72:125-32.
20. White N, Litovitz T, Clancy C. Suicidal antidepressant overdoses: a comparative analysis by antidepressant type. J Med Toxicol 2008;4:238-50.
21. Yilmaz Z, Ceschi A, Rauber-Luethy C, et al. Escitalopram causes fewer seizures in human overdose than citalopram. Clin Toxicol 2010;48:207-12.
22. Balit CR, Lynch CN, Isbister GK. Bupropion poisoning: a case series. Med J Aust 2003;178:61-3.
23. Serena-Zach S. Acute maprotiline intoxication: symptomes, dose-effect relationship and decontamination [MD Thesis]. University of Zürich, Switzerland; 1993. Available at: http://www.toxi.ch/upload/pdf/Diss_Serena_1993.pdf. Accessed on 30 January 2014.
24. Chan AN, Gunja N, Ryan CJ. A comparison of venlafaxine and SSRIs in deliberate self-poisoning. J Med Toxicol 2010;6:116-21.

25. Colbridge MG, Volans GN. Venlafaxine in overdose - experience of the national poisons information service (London Centre). J Toxicol Clin Toxicol 1999;37:383.
26. Kelly CA, Dhaun N, Laing WJ, Strachan FE, Good AM, Bateman DN. Comparative toxicity of citalopram and the newer antidepressants after overdose. J Toxicol Clin Toxicol 2004;42:67-71.
27. Whyte IM, Dawson AH, Buckley NA. Relative toxicity of venlafaxine and selective serotonin reuptake inhibitors in overdose compared to tricyclic antidepressants. QJM 2003;96:369-74.
28. Hayes BD, Klein-Schwartz W, Clark RF, Muller AA, Miloradovich JE. Comparison of toxicity of acute overdoses with citalopram and escitalopram. J Emerg Med 2010;39:44-8.
29. Personne M, Persson H, Sjoberg E. Citalopram toxicity. Lancet 1997;350:518-9.
30. Waring WS, Gray JA, Graham A. Predictive factors for generalized seizures after deliberate citalopram overdose. Br J Clin Pharmacol 2008;66:861-5.
31. Court H, Volans GN. Poisoning after overdose with non-steroidal anti-inflammatory drugs. Adverse Drug React Acute Poisoning Rev 1984;3:1-21.
32. Graf BC. Die akute Intoxikation mit Ponstan® [MD Thesis]. University of Zürich, Switzerland; 1994.
33. Laredo PB. Die akute Intoxikation mit Ponstan [MD Thesis]. University of Zürich, Switzerland; 2007. Available at: http://www.toxi.ch/upload/pdf/Laredo_Mefenaminsaeure_2007.pdf. Accessed on 30 January 2014.
34. Montgomery SA. Antidepressants and seizures: emphasis on newer agents and clinical implications. Int J Clin Pract 2005;59:1435-40.
35. Jain R, Balhara YP. Impact of alcohol and substance abuse on adolescent brain: a preclinical perspective. Indian J Physiol Pharmacol 2010;54:213-34.
36. Priel MR, dos Santos NF, Cavalheiro EA. Developmental aspects of the pilocarpine model of epilepsy. Epilepsy Res 1996;26:115-21.
37. Singleton MW, Holbert WH, 2nd, Ryan ML, Lee AT, Kurz JE, Churn SB. Age dependence of pilocarpine-induced status epilepticus and inhibition of CaM kinase II activity in the rat. Brain Res Dev Brain Res 2005;156:67-77.
38. Forsgren L, Beghi E, Oun A, Sillanpaa M. The epidemiology of epilepsy in Europe - a systematic review. Eur J Neurol 2005;12:245-53.
39. Gutscher K, Rauber-Luthy C, Haller M, et al. Patterns of toxicity and factors influencing severity in acute adult trimipramine poisoning. Br J Clin Pharmacol 2013;75:227-35.
40. Sharma AN, Hoffman RJ. Toxin-related seizures. Emerg Med Clin North Am 2011;29:125-39.
41. Hoffman RS. Understanding the limitations of retrospective analyses of poison center data. Clin Toxicol 2007;45:943-5.

Age [years]	All cases*	All Cases [%]	Cases with seizures*	Cases with seizures [%]	Seizure rate [%]	95% Confidence interval	
						Lower bound [%]	Upper bound [%]
0-4	3646	24.4	14	4.6	0.4	0.2	0.6
5-9	359	2.4	2	0.7	0.6	0.2	2.0
10-14	639	4.3	12	3.9	1.9	1.1	3.3
15-19	1934	13.0	83	27.3	4.3	3.5	5.3
20-99	8349	55.9	193	63.5	2.3	2.0	2.7
0-99	14927	100.0	304	100.00	2.0	1.8	2.3

Table 1

Drug	Number of seizures	Seizures in [%] of all seizures
Antidepressants	**136**	**43.5**
TCAs	50	16.0
SSRIs	47	15.0
Venlafaxine	23	7.3
Maprotiline	10	3.2
Bupropion	6	1.9
Antipsychotics	**30**	**9.6**
Quetiapine	10	3.2
Chlorprothixene	8	2.6
Clozapine	4	1.3
Olanzapine	3	1.0
Clotiapine	2	0.6
Flupentixol	1	0.3
Levomepromazine	1	0.3
Promazine	1	0.3
Antiepileptics	**17**	**5.4**
Carbamazepine	11	3.5
Lamotrigine	2	0.6
Tiagabine	1	0.3
Oxcarbazepine	1	0.3
Valproic acid	1	0.3
Phenytoin	1	0.3

Table 2

Drug	Cases	Dose range [g]	Median dose [g]
Mefenamic acid	all	0.1-45.0	6.0
	with seizures	4.5-36.0	8.5
Citalopram	all	0.01-4.0	0.4
	with seizures	0.28-2.4	1.1
Trimipramine	all	0.01-30.0	1.1
	with seizures	0.35-10.0	2.0
Venlafaxine	all	0.038-29.4	1.5
	with seizures	1.2-22.0	4.0

Table 3

Captions of tables

Table 1. Age distribution of cases with and without seizures and seizure rates.

*Precise age was not known in 514 of all cases and in 9 of the cases with seizures.

Table 2. Seizure rates in different drug classes. The table indicates the absolute number of seizures and the percentage in relation to all 313 cases with seizures. TCAs=tricyclic antidepressants, SSRIs= selective serotonin reuptake inhibitors.

Table 3. Dose ranges and medians of ingested doses of the pharmaceuticals associated with more than 20 cases with seizures.

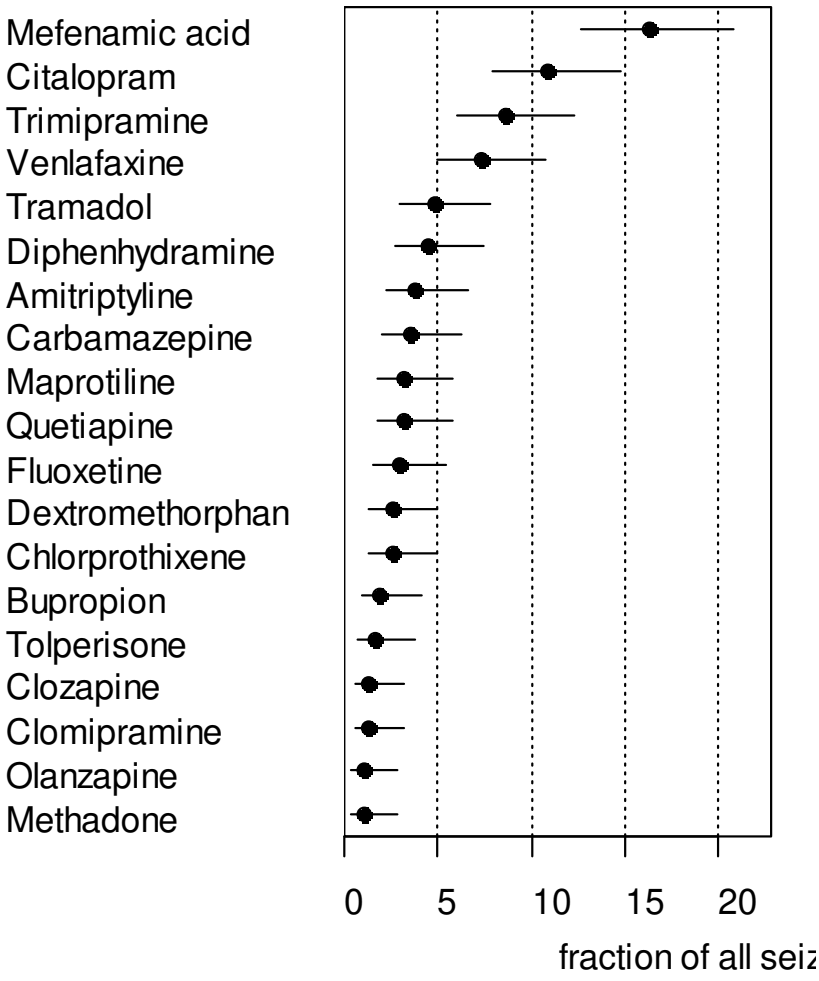
Mefenamic acid
Citalopram
Trimipramine
Venlafaxine
Tramadol
Diphenhydramine
Amitriptyline
Carbamazepine
Maprotiline
Quetiapine
Fluoxetine
Dextromethorphan
Chlorprothixene
Bupropion
Tolperisone
Clozapine
Clomipramine
Olanzapine
Methadone
0
5
10
15
20
fraction of all seiz

Figure 1

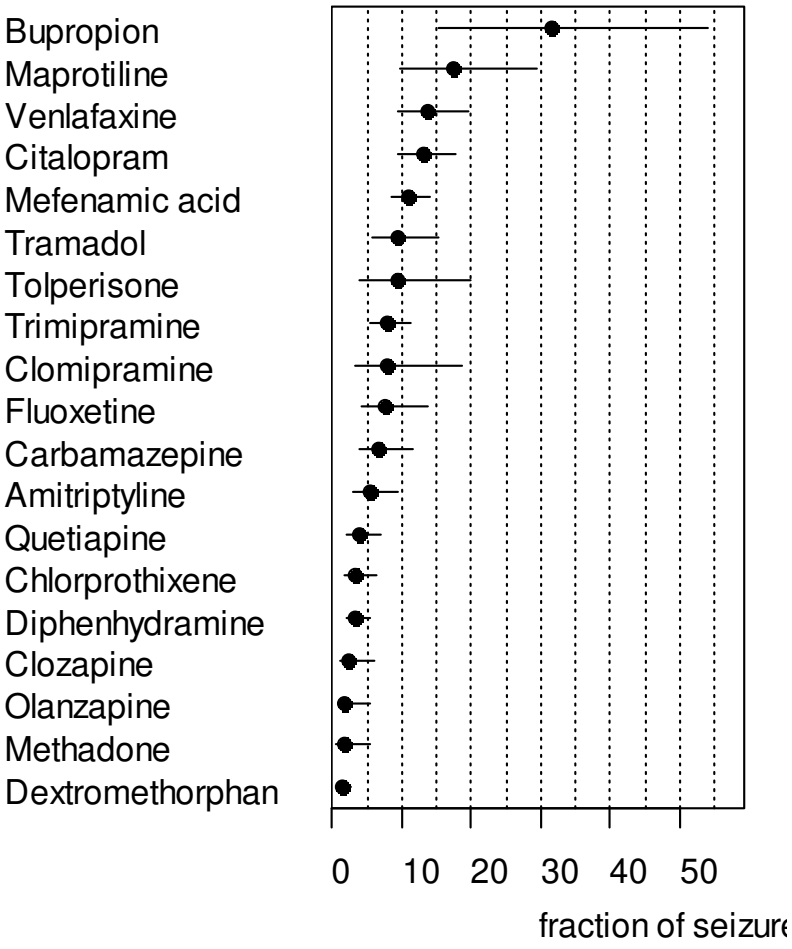
Bupropion
Maprotiline
Venlafaxine
Citalopram
Mefenamic acid
Tramadol
Tolperisone
Trimipramine
Clomipramine
Fluoxetine
Carbamazepine
Amitriptyline
Quetiapine
Chlorprothixene
Diphenhydramine
Clozapine
Olanzapine
Methadone
Dextromethorphan
0
10
20
30
40
50
fraction of seizure

Figure 2

Captions of figures

Figure 1. Pharmaceutical drugs associated with ≥ 3 cases with seizures. Lines correspond to 95% confidence intervals. For all involved pharmaceuticals see online supplementary data.

Figure 2. Seizure potential of pharmaceuticals in overdose. Lines correspond to 95% confidence intervals.

Pharmaceuticals	Number of all cases with a pharma-ceutical	Number of cases with seizures	Seizures in [%] of all 313 cases with seizures (see also Figure 1)	95% Confidence interval	
				Lower bound [%]	Upper bound [%]
Mefenamic acid	470	51	16.3	12.6	20.8
Citalopram	259	34	10.9	7.9	14.8
Trimipramine	336	27	8.6	6.0	12.3
Venlafaxine	168	23	7.3	4.9	10.8
Tramadol	157	15	4.8	2.9	7.8
Diphenhydramine	429	14	4.5	2.7	7.4
Amitriptyline	220	12	3.8	2.2	6.6
Carbamazepine	163	11	3.5	2.0	6.2
Maprotiline	57	10	3.2	1.7	5.8
Quetiapine	256	10	3.2	1.7	5.8
Fluoxetine	118	9	2.9	1.5	5.4
Chlorprothixene	245	8	2.6	1.3	5.0
Dextromethorphan	586	8	2.6	1.3	5.0
Bupropion	19	6	1.9	0.9	4.1
Tolperisone	54	5	1.6	0.7	3.7
Clomipramine	50	4	1.3	0.5	3.2
Clozapine	164	4	1.3	0.5	3.2
Methadone	162	3	1.0	0.3	2.8
Olanzapine	156	3	1.0	0.3	2.8
Bupivacaine	4	2	0.6	0.2	2.3
Clotiapine	81	2	0.6	0.2	2.3
Codeine	70	2	0.6	0.2	2.3
Dibenzepin	3	2	0.6	0.2	2.3
Doxepin	22	2	0.6	0.2	2.3
Fluvoxamine	42	2	0.6	0.2	2.3
Ioxaglic acid	2	2	0.6	0.2	2.3
Isoniazid	8	2	0.6	0.2	2.3
Lamotrigine	55	2	0.6	0.2	2.3
Lidocaine	13	2	0.6	0.2	2.3
Opipramol	27	2	0.6	0.2	2.3
Phenobarbital	88	2	0.6	0.2	2.3
Propranolol	58	2	0.6	0.2	2.3
Verapamil	33	2	0.6	0.2	2.3
Amine compounds	1	1	0.3	0	1.8
Aminophylline	4	1	0.3	0	1.8
Atropine	35	1	0.3	0	1.8
Barium	4	1	0.3	0	1.8
Biperiden	28	1	0.3	0	1.8
Chloral hydrate	59	1	0.3	0	1.8
Cyclopentolate	3	1	0.3	0	1.8
Dapsone	4	1	0.3	0	1.8
Dosulepin	6	1	0.3	0	1.8
Fluoride	11	1	0.3	0	1.8
Flupentixol	43	1	0.3	0	1.8
Glibenclamide	6	1	0.3	0	1.8

Ketamine	5	1	0.3	0	1.8
Levomepromazine	146	1	0.3	0	1.8
Methaqualone	16	1	0.3	0	1.8
Metoclopramide	57	1	0.3	0	1.8
Midazolam[1]	126	1	0.3	0	1.8
Morphine	65	1	0.3	0	1.8
Oxcarbazepine	12	1	0.3	0	1.8
Paroxetine	115	1	0.3	0	1.8
Phenytoin	28	1	0.3	0	1.8
Promazine	104	1	0.3	0	1.8
Propafenone	3	1	0.3	0	1.8
Sertraline	150	1	0.3	0	1.8
Thiopental	1	1	0.3	0	1.8
Tiagabine	1	1	0.3	0	1.8
Valproic acid	120	1	0.3	0	1.8
Zolpidem[2]	630	1	0.3	0	1.8

Table Online supplementary data

Captions online supplementary data

Table. Pharmaceutical drugs associated with seizures. [1]Focal twitching after application of flumazenil. [2]Seizure reported, but not witnessed by a medical professional